CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S010

MEDICAL REVIEW(S)

Oliver

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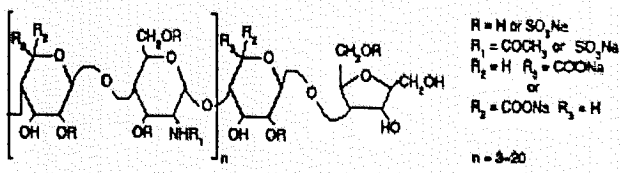
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-287/ S-010
Drug name:	Fragmin
Generic name:	Dalteparin Sodium
Other names:	FR-860, Heparin fragment Kabi-2165, Kabi 2165, Tedelparin
Chemical name:	Nitrous acid degradation product of porcine intestinal mucosa. Majority of components have a 2-0-sulpho-alpha-L- idophyanosuronic reducing end of their chain
Structure:	
Sponsor:	Pharmacia & Upjohn, Kalamazoo, Michigan
Pharmacologic Category:	Anticoagulant and Antithrombotic Low Molecular Weight Heparin
Proposed Indications:	Unstable angina and non-Q-wave myocardial infarction
Dosage Form(s) and Route(s) of Administration:	120 IU/kg (Max 10,000U/dose) s.c. every 12 hours In conjunction with aspirin
Important Related Drugs:	Enoxaparin (Lovenox®) Ardeparin (Normiflo®) Danaparoid (Orgaran®)
Related reviews:	NDA 20-287, NDA 20-287/S-008, IND [redacted]
Date of Submission: **Date received by HFD-180:** **Date of Review:**	May 29, 1998 June 1, 1998 February 11, 1999
Medical Reviewer:	John William Schmeling, M.D., Ph.D.

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ACRONYMS and ABBREVIATIONS

AE	Adverse event
AMI	Acute myocardial infarction
ASA	Aspirin
aXa	Anti activated factor X
b.i.d.	Twice a day
CABG	Coronary artery bypass grafting
CK	Creatinine kinase
CK-MB	Creatinine kinase, MB band
CMH	Cochran-Mantel-Haenszel
GCP	Good clinical practice
GCP	Good clinical practice
GI	Gastrointestinal
IRB	Institutional review board
ITT	Intention to treat
IU	International units
LMWH	Low molecular weight heparin
LVT	Left ventricular thrombus
MI	Myocardial infarction
mV	Millivolt
p.o.	By mouth
PP	Per protocol
PTCA	Percutaneous transluminal coronary artery angioplasty
PTT	Partial thromboplastin time
q.d.	Every day
s.c.	Subcutaneously
s.d.	Standard deviation
SK	Streptokinase
t.i.d.	Three times a day
UFH	Unfractionated heparin

1. MATERIAL UTILIZED IN REVIEW

1.1 Materials from NDA/IND

A supplemental application, S-010, to NDA 20,287, consisting of 86 volumes was reviewed.

1.2 Related Review, Consults

The medical officer's reviews of IND [redacted], NDA 20-287, and NDA 20-287/S-008 and the statistician's review of the current submission were reviewed.

2. BACKGROUND

2.1 Indication

The sponsor has submitted two different indications. The indication stated on form FDA 356h is "Unstable angina and non-Q-wave myocardial infarction." However, the proposed labeling states that "Fragmin® is indicated for the treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concomitant aspirin."

2.2 Rationale

2.2.1 Background for Treatment of Unstable Coronary Artery Disease

The sponsor cites two background studies, The RISC trial, and Théroux's Canadian study.

2.2.1.1 RISC trial[1]

The RISK trial enrolled 796 men with unstable coronary artery disease (unstable angina or non-Q-wave myocardial infarction) into a double-blind placebo-controlled study. They were treated with oral aspirin (75 mg/day for a year) and/or 5 days of intermittent intravenous heparin (10000 U iv every 6 hours for 24 hours, then 7500 U every 6 hours for four days without titration to PTT). The risk of MI and deaths was reduced by aspirin. Heparin had no

significant influence on event rate, although the group treated with aspirin and heparin had the lowest number of events during the initial 5 days.

Figure 1: RISC trial results [1]

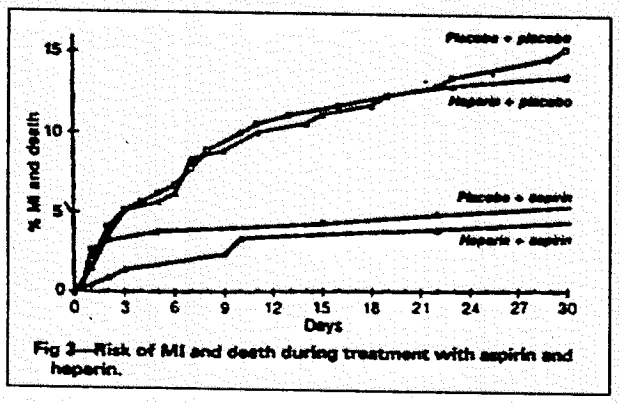

Fig 3—Risk of MI and death during treatment with aspirin and heparin.

Aspirin significantly reduced MI and death. Heparin had no significant effect. The sponsor notes that by day five heparin plus aspirin had a significant effect but that aspirin alone did not. However, it was also true at day five that placebo/aspirin was not significantly different from heparin/aspirin.

2.2.1.2 Théroux et. al., the Canadian study[2]

Patients (479) were randomized to a placebo-controlled, short-term study comparing the effectiveness of aspirin, heparin or aspirin/heparin, in the treatment of unstable angina.

Aspirin was given at a higher dose than the RISC study (650 mg initially and then 325 mg bid), and heparin was given as a constant infusion and at a different dose (given as a 5000 unit bolus followed by 1000U/hr titrated to 1.5-2 times control PTT). Patients were studied for a maximum of nine days.

Myocardial infarction, compared to placebo, was decreased significantly in all three groups (aspirin, aspirin/heparin, heparin).

Further analysis of these patients showed that there was a significant "reactivation" of disease in the group treated with heparin alone shortly (a

few days) after cessation of heparin. This did not occur in the aspirin or aspirin/heparin groups.[3]

2.2.2 Rationale for using Fragmin® to treat unstable coronary artery syndromes

Fragmin® is currently approved in the United States for prophylaxis against deep vein thrombosis in patients undergoing abdominal surgery who are at risk for thromboembolic complications. Fragmin® is approved in other countries for the treatment of acute deep venous thrombosis, prevention of clotting in the extracorporeal circulation during hemodialysis, acute and prolonged thromboprophylaxis in surgery, and treatment of unstable angina or non-Q-wave myocardial infarction.

The sponsor contrasts low molecular weight heparins (LMWHs) to unfractionated heparin (UFH) and states that Fragmin is superior in the following respects:

1. Increased bioavailability and longer plasma half-life allow LMWHs to provide a predictable anticoagulant response when administered at fixed does once or twice daily.
2. Fragmin® is rapidly and almost completely absorbed from the subcutaneous depot and can be administered without the need for continuous monitoring.
3. Long-term treatment with Fragmin® is well tolerated.
4. Fragmin® affects platelet function to a lesser extent than heparin.
5. Fragmin® releases lipoprotein lipase to a lesser extent that unfractionated heparin and may be preferred in clinical situations in which high plasma lipolytic activity is a disadvantage.

2.2.3 Rationale for Fragmin® dosage, acute phase and chronic phase

The studies cited by the sponsor to support their choice of dosing regimens are summarized in Table 1.

2.2.3.1 Acute phase

The sponsor states that the dosing schedule was based on experience with Fragmin in prophylaxis of ventricular thrombosis after acute myocardial infarction.

Studies by Nesvold [5] and others used doses of 150 IU/k.g. twice daily, while Scala et. al [4] used 120 IU./k.g.

The FRISC trial initially started with a dose of 150 IU/k.g. / 12 hours.

Because of significant bleeding, the trial was halted after 116 patients had been treated and the randomization code for 10 patients was broken.

The trial was then restarted at a dose of 120 IU/k.g. /12 hours.

2.2.3.2 Chronic phase

The dosage chosen for the chronic phase was based on the use of Fragmin in the long-term prophylaxis of thromboembolism after high-risk surgery.

2.3 Administrative History

A new Drug Application for Fragmin® was submitted August 6, 1992, resubmitted December 22, 1992, and finally approved on December 22, 1994, for the following indication at a dose of 2500 IU/s.c. q.d.:

> "The prophylaxis of deep venous thrombosis, which may lead to pulmonary embolism, in patients undergoing abdominal surgery who are at risk of thromboembolic complications. Patients at risk include patients who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism."

Supplement 003, submitted July 7, 1995, was approved March 18, 1996, and provided for the following:

> "a 5000 IU dose for the prophylaxis against deep venous thrombosis, which may lead to pulmonary embolism, inpatients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignancy disorder."

Table 1: The studies that the sponsor cites to support their dosing regimens

Study	G	Type of study	Patients			Fragmin® dose and other treatments	Endpoints	Results	Safety
			# Total Randomized # Fragmin/ Control # / total	Age (mean or median) (range)	Type				
Studies cited in support of the acute phase of the study.									
Scala[4]	U	Open label, randomized, heparin (continuous infusion, PTT 1.5-2.5 times control).	39 13/12 30/9		AMI of less than 48h	120 IU/kg b.i.d. s.c. for 7 days	Occurrence of DVT, left ventricular thrombus.	No difference in DVT or thrombus (none in either group). Study too small to draw conclusions. No statistical comparison done.	7 day exposure One patient in Fragmin® group ha moderate GI bleed. 1 patient in heparin group had acut anemia without externa bleeding. 3 in each group died of cardiac arrest.
Nesvold[5]	N	Open, non-randomized, dose-finding study.	72 NA 61/11	66 38-75	AMI	Multiple regimens. 240-360 IU/kg/day sc. bid or tid for 6-10 days some in combination with SK and/or ASA	1° Define a Fragmin dosage in patients with AMI aiming at anti-Xa levels of 0.6-1.0 IU/ml 2° The frequency of left ventricular thrombus as defined by echocardiogram	300 U/kg/day of Fragmin ®, given bid or tid, thought to be safe with respect to bleeding. Lower incidence of LV thrombus compared to historical controls. No statistical analysis done	6-10 day exposure 300 U/kg/day of Fragmin ®, given bi or tid, thought to be safe wit respect to bleeding. 4 minor bleeds (all in Fragmin® an or SK/ASA group)
FRAMI STUDY Dale[6]	U	Randomized, double-blind, placebo-controlled, parallel-group, multi-center	776 338/338 569/207	63±12 s.d. NA	AMI	Fragmin ® 150 IU/bid s.c. every 12 h for 10 days Some with SK Warfarin or ASA	1° Incidence of LVT 2° Incidence of reinfarction, cardo- or cerebro/vascular mortality, safety.	No significant differences	Major bleeds higher in Fragmin group 2.8% vs. 0.3% (p 0.004). Minor bleeds also higher in Fragmin group 13.6% vs. 1.8% p 0.001
Nilsen[7]	U	Prospective, active comparator, randomized, open study.	100 36/36 74/22	64±11 s.d. NA	AMI	150 IU or 100 IU /kg s.c. vs. Heparin 12,500 bid s.c. for 7 days All patients got ASA 160 p.o. q.d. and SK 1.5 mill IU over 1 hour	1° Safety 2° Coagulation, incidence of reinfarction death	No significant differences	Significant bleeding in the 150 IU Group. Dose changed to 100 IU mi study.
Studies cited in support of the chronic phase of the study									

[1] Good Clinical Practices: N=no, Y=yes, U=unknown.

Study	G	Type of study	Patients			Fragmin® dose and other treatments	Endpoints	Results	Safety
			# Total Random # Fragmin/ Control # / total	Age (mean or median) (range)	Type				
Harenberg[8]	U	Prospective, no controls	70 NA NA	56 25-80	Indication for prophylaxis from thromboembolic event and a history of treatment with oral anticoagulant or heparin who had had problems	100 IU/kg or 140 IU/kg s.c. once a day, based on risk of patient It appears that doses were then titrated based on plasma aXa activity Average dose 7500 IU/day Range 2500-15000 IU/day Mean treatment period 26 weeks	Observational study	5 thromboembolic events	31-month exposure with over %50 o the subjects dropped out by and only 2 patients still i study at month 31. No fatal or severe bleeding. Nin episodes of minor bleeding

Table Constructed by Medical Officer

2.4 Foreign experience

According to the sponsor, Dalteparin is marketed in 48 countries world-wide for use in thromboprophylaxis during hemodialysis, general and orthopedic surgery, and in disseminated intravascular coagulation and is approved for use in unstable coronary artery syndromes in Australia, Austria, Cyprus, Denmark, Finland, The Netherlands, New Zealand, Norway, South Africa, Sweden and the United Kingdom (Page 8/29/311-314).

2.5 Current FDA approved use in the United States

Fragmin is currently used for the prophylaxis against deep venous thrombosis, which may lead to pulmonary embolism, in patients undergoing abdominal surgery and in patients undergoing hip replacement. The current dosing labeling is as follows.

2.5.1 Abdominal Surgery

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN Injection is 2500 IU administered by subcutaneous (s.c.) injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily for 5 to 10 days postoperatively. In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily for 5 to 10 days postoperatively. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c.1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily for 5 to 10 days postoperatively.

2.5.2 Hip Replacement Surgery

In patients undergoing hip replacement surgery, the recommended first dose of FRAGMIN is 2500 IU administered by s.c. injection within 2 hours before surgery and the second dose of 2500 IU s.c. in the evening of the day of surgery (at least 6 hours after the first dose). If surgery is performed in the evening, omit the second dose on the day of surgery. Starting on the first postoperative day, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. Alternatively, 5000 IU of FRAGMIN can be administered the evening before surgery, followed by 5000 IU once daily, starting in the evening of the day of surgery. Up to 14 days of

treatment was well tolerated in controlled clinical trials, where the average duration of treatment was 5 to 10 days postoperatively.

3. REVIEW OF INDIVIDUAL STUDIES

3.1 Overview of studies submitted

The studies included in this submission are summarized in Table 2.

3.1.1 FRISC

FRISC, the first of two pivotal studies in this submission, was a prospective, randomized, double blind, placebo-controlled, parallel group, multi-center study in patients with unstable coronary artery syndromes (unstable angina or non-Q-wave MI).

Phase I (day 1-6) and Phase II (day 6-45) both compared Fragmin/ASA treatment versus placebo/ASA.

The primary endpoint of the study was death and/or myocardial infarction during the first 6 days of treatment.

3.1.2 FRIC

FRIC, the second of two pivotal studies in this submission, was a prospective, randomized, controlled parallel group multi-center, two-phase study, in patients with unstable coronary artery syndromes (unstable angina or non-Q-wave MI).

Phase I (day 1-6) was open label and Phase II (day 6-45) was double-blinded.

Phase I compared Fragmin/ASA to heparin/ASA. Phase II compared Fragmin/ASA to placebo/ASA.

The primary endpoint was the incidence of death, myocardial infarction and/or recurrence of angina during Phase II.

3.1.3 FRISC II

FRISC II is an ongoing prospective, randomized, parallel-arm, multi-center, two-phase trial, in patients with unstable coronary artery syndromes (unstable angina or non-Q-wave MI).

Phase I (day 1 to day 5-7) is open-label Fragmin/ASA for all patients. Phase II (day 6-90) is a double-blind comparison of Fragmin/ASA and placebo/ASA.

The primary endpoints are death or myocardial infarction after 3 and 6 months.

3.1.4 FRAMI

FRAMI was a prospective, placebo-controlled, randomized, double blind, parallel arm study, in patients with their first anterior-wall myocardial infarction.

Patients were treated with Fragmin/ASA or placebo/ASA for 10 days.

90% of the patients also received streptokinase.

The primary endpoints were left-ventricular thrombus and arterial emboli.

3.1.5 Other studies

TRN91-111 was a prospective, open-label, randomized pilot study in patients with acute myocardial infarctions who were also treated with streptokinase.

CTN 88-009 was an uncontrolled dose-finding study.

TRN 88-084 was an open trial comparing Fragmin and streptokinase to streptokinase alone in patients with acute myocardial infarctions.

BIOMACS II was a randomized, double blind, placebo-controlled, parallel-group, multi-center, pilot study comparing Fragmin to placebo before and after streptokinase in patients with acute myocardial infarctions.